Selective requirement of PI3K/PDK1 signaling for Kras oncogene-driven pancreatic cell plasticity and cancer.

Oncogenic Kras activates a plethora of signaling pathways, but our understanding of critical Ras effectors is still very limited. We show that cell-autonomous phosphoinositide 3-kinase (PI3K) and 3-phosphoinositide-dependent protein kinase 1 (PDK1), but not Craf, are key effectors of oncogenic Kras in the pancreas, mediating cell plasticity, acinar-to-ductal metaplasia (ADM), and pancreatic ductal adenocarcinoma (PDAC) formation. This contrasts with Kras-driven non-small cell lung cancer, where signaling via Craf, but not PDK1, is an essential tumor-initiating event. These in vivo genetic studies together with pharmacologic treatment studies in models of human ADM and PDAC demonstrate tissue-specific differences of oncogenic Kras signaling and define PI3K/PDK1 as a suitable target for therapeutic intervention specifically in PDAC.